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**Association of Persistent or Worsened Echocardiographic Dyssynchrony with
Unfavorable Clinical Outcomes in Heart Failure Patients with Narrow QRS Width:
A Subgroup Analysis of the EchoCRT Trial**

Short title: Association of dyssynchrony on outcomes in narrow QRS

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John Gorcsan III, M.D.¹, Peter Sogaard, M.D., D.M.Sc.², Jeroen J. Bax, M.D., Ph.D.³, Jagmeet P.
Singh, M.D.⁴, William T. Abraham, M.D., Ph.D.^{5*}, Jeffrey S. Borer, M.D.⁶, Kenneth Dickstein,
M.D., Ph.D.⁷, Daniel Gras, M.D.⁸, Henry Krum, M.B., B.S., Ph.D.⁹, Josep Brugada, M.D.¹⁰,
Michele Robertson, Bsc¹¹, Ian Ford, Ph.D.¹¹, Johannes Holzmeister, M.D.¹²,
and Frank Ruschitzka, M. D.^{13*}

¹ University of Pittsburgh, Pittsburgh (J.G.), ² Aalborg University, Aalborg, Denmark (P.S) ³ Leiden University Medical Center, Leiden, the Netherlands (J.B.), ⁴ Massachusetts General Hospital, Harvard Medical School, Boston (J.S.), ⁵ Division of Cardiovascular Medicine, Ohio State University Medical Center, Davis Heart and Lung Research Institute, Columbus (W.A.), ⁶ Department of Cardiology, Division of Cardiovascular Medicine and Howard Gilman and Ron and Jean Schiavone Institutes, State University of New York Downstate College of Medicine, New York (J.B.), ⁷ University of Bergen, Stavanger University Hospital, Stavanger, Norway (K.D.), ⁸ Nouvelles Cliniques Nantaises, Nantes, France (D.G.), ⁹ Monash Centre of Cardiovascular Research and Education in Therapeutics, Melbourne, VIC, Australia (H.K.), ¹⁰ Cardiology Department, Thorax Institute, Hospital Clinic, University of Barcelona, Barcelona, Spain, ¹¹ Robertson Centre for Biostatistics, University of Glasgow, Glasgow, United Kingdom, ¹³ Department of Cardiology, University Heart Center Zurich, Switzerland,

Correspondence:

John Gorcsan III, MD

University of Pittsburgh, Scaife 564, 200 Lothrop Street, Pittsburgh, PA 15213-2582

Phone: 412- 647-6570

Fax: 412- 647-0568

E-mail: gorcsanj@upmc.edu

Abstract

Aims: EchoCRT was a randomized trial of cardiac resynchronization therapy (CRT) in severely symptomatic heart failure (HF) patients with narrow QRS width $< 130\text{ms}$, ejection fraction (EF) $\leq 35\%$ and echocardiographic dyssynchrony. All received CRT implants which were then randomized to CRT-On or CRT-Off. While the trial showed no benefit of CRT to these patients, the aim of this subgroup analysis was to test the hypothesis that persistent or worsening dyssynchrony is associated with unfavorable clinical outcomes.

Methods and Results: We studied 614 EchoCRT patients with baseline and 6 month echocardiograms. Baseline dyssynchrony required for study inclusion was either tissue Doppler imaging longitudinal velocity delay $\geq 80\text{ ms}$, or speckle tracking radial strain delay $\geq 130\text{ ms}$. Persistent dyssynchrony at 6 months was observed similarly in both groups (77% in CRT-On; 76% in CRT-Off). Persistent dyssynchrony was associated with a significantly higher primary end-point of death or HF hospitalization, (HR=1.54, 95% CI 1.03-2.30, $p=0.03$), and in particular secondary endpoint of HF hospitalization (HR=1.66, 95% CI 1.07-2.57, $p=0.02$). HF hospitalizations were also associated with worsening longitudinal dyssynchrony (HR=1.45, 95% CI 1.02-2.05, $p=0.037$), and worsening radial dyssynchrony (HR=1.81, 95% CI 1.16-2.81, $p=0.008$). Associations of persistent or worsening dyssynchrony with outcomes were similar in CRT-Off and CRT-On groups.

Conclusions: Persistent or worsening echocardiographic dyssynchrony in HF patients with narrow QRS width was a marker for unfavorable clinical outcomes unaffected by CRT. In particular, echocardiographic dyssynchrony on follow-up was strongly associated with HF hospitalizations and appears to be a prognostic marker of disease severity.

Key Words: Heart failure, echocardiography, cardiac resynchronization therapy

Introduction

Cardiac resynchronization therapy (CRT) has been an important advance in the treatment of heart failure (HF) patients with reduced left ventricular (LV) ejection fraction (EF) and QRS widening.¹⁻³ Many studies have demonstrated that HF patients with widened QRS who have measureable differences in timing of regional LV contraction, known as mechanical dyssynchrony, have a more favorable response to CRT than those without dyssynchrony.⁴⁻⁹ Mechanical dyssynchrony is also commonly observed in HF patients with reduced LVEF without QRS widening.¹⁰⁻¹³ EchoCRT tested the hypothesis that CRT may benefit HF patients with narrow QRS width (<130ms) and echocardiographic dyssynchrony in a large multicenter randomized controlled clinical trial.¹⁴ Patients qualified for EchoCRT with New York Heart Association (NYHA) Class III or ambulatory Class IV HF with LVEF $\leq 35\%$, increased LV end-diastolic diameter (LVEDD) ≥ 55 mm, and dyssynchrony by either tissue Doppler imaging (TDI) longitudinal velocity or speckle tracking radial strain before randomization. The main trial randomized 809 patients from 115 centers. EchoCRT was prematurely terminated due to futility in affecting the primary combined end-point of death or HF hospitalization and for an observed increased mortality in patients with CRT-On. EchoCRT concluded that CRT does not benefit HF patients with mechanical dyssynchrony without QRS widening.

Physiological studies have shown that mechanical dyssynchrony impairs LV ejection efficiency.¹⁵⁻¹⁷ However, the prognostic significance of mechanical dyssynchrony in HF patients with narrow QRS width and reduced LVEF remains unclear. Furthermore, dyssynchrony has been observed to change overtime and may relate to the underlying disease process.¹⁸ Accordingly, the aim of this EchoCRT substudy analysis was to test the hypothesis that persistent or worsening echocardiographic dyssynchrony is associated with unfavorable clinical outcomes, in comparison to HF patients who improve dyssynchrony over time. A second aim was to test for the potential for an interaction of CRT treatment on persistent or worsening

dyssynchrony and clinical outcomes. This EchoCRT subgroup consisted of patients with follow-up echocardiograms for dyssynchrony analysis at 6 months after randomization.

Methods

Patient Selection

The study was compliant with institutional review board or ethics panel review and all patients provided written informed consent. All patients were 18 years of age or older, with NYHA class III or IV HF on stable medical therapy; QRS duration ≤ 130 ms; a LVEDD ≥ 55 mm a standard indication for an implantable cardioverter–defibrillator (ICD) and echocardiographic evidence of LV dyssynchrony. Dyssynchrony was defined by means of color-coded TDI as an opposing-wall delay in the peak systolic velocity of ≥ 80 ms in apical 4 chamber or apical long-axis views^{5,7} or by means of speckle-tracking radial strain as a delay in the anteroseptal-to-posterior wall of ≥ 130 ms or more in the mid-LV short-axis view.¹⁹ Patients were excluded with acute decompensated HF, intravenous inotropic therapy, atrial fibrillation within the previous month, or bradycardia requiring pacing. Patients were implanted with a CRT and defibrillator (CRT-D) (Biotronik Lumax, Berlin, Germany) with LV leads placed through epicardial coronary veins targeting the posterior or lateral free wall. Patients with successful CRT-D implantation were equally randomized to CRT-On or CRT-Off groups. The cohort for the present study consisted of 614 patients who had echocardiography at baseline and at 6 months follow-up after randomization. The flow chart (Figure 1) shows the details of patients included in this substudy.

Echocardiographic Dyssynchrony Analysis

Quantitative echocardiographic analysis was performed using identical methods at baseline and at 6 month follow-up at the University of Pittsburgh echo core lab by investigators blinded to randomization and all other clinical data. All sites had formal training classes requiring certification of site individuals for image acquisition and analysis, and screening analysis was performed by on-site investigators, with confirmatory qualifying analysis performed by the core

lab.¹⁴ Acquisition used a uniform ultrasound system vendor (GE Vivid 7 or E9, Horton, Norway) and analysis software (GE EchoPAC version BT08-09, Horton, Norway). Off-line dyssynchrony analysis by TDI was applied to apical 4 chamber and apical long axis views using color coding of the time to peak velocity (tissue synchronization imaging)⁵ and high frame rates (> 100Hz). (Figure 2) Two 7 x 15 mm regions of interest were applied to septal and opposing walls of 4-chamber and apical long axis views in basal and mid segments.²⁰ The maximal time difference in peak longitudinal velocity from opposing walls between aortic valve opening and aortic valve closure was averaged from 3 or more beats. Dyssynchrony by speckle tracking radial strain was assessed from the mid-LV short axis views at frame rates 60-90 Hz. Regions of interest were manually drawn on the endocardial and epicardial borders. The regions of interest were manually adjusted to optimize the timing of peak septal thickening (in either antero-septal or septal segments) and posterior wall segments and averaged from 3 or more beats. Either a TDI opposing wall longitudinal velocity delay ≥ 80 ms or a speckle tracking radial strain septal to posterior wall delay ≥ 130 ms was required for qualification for EchoCRT.

Change in Dyssynchrony from Baseline to 6 Month Follow-Up

The same pre-defined criteria for significant dyssynchrony at baseline above were used at 6 months. Criteria for worsening dyssynchrony were derived post hoc. Worsening dyssynchrony at 6 months by TDI longitudinal septal to lateral wall delay as an increase by ≥ 30 ms (approximately 40% greater than the baseline entry criterion of 80 ms). Worsening dyssynchrony at 6 months by radial strain septal to posterior wall delay by defined as an increase by ≥ 60 ms (approximately 50% greater than the baseline entry criterion of 130ms). A 10% greater increase in radial strain delay than in TDI velocity delay was chosen to indicate worsening dyssynchrony to account for the higher variability in speckle tracking radial strain.

Echocardiographic Dyssynchrony Variability Analysis

The inter-observer variability of physicians in the core laboratory in a sample of 50 randomly

selected EchoCRT echocardiograms as previously reported had agreement for dyssynchrony as follows: TDI opposing wall delay apical 4-chamber view 96% (kappa coefficient 0.92), TDI opposing wall delay apical long-axis view 92% (kappa coefficient 0.84), and speckle tracking radial strain septal to posterior wall delay 90% (kappa coefficient 0.79), as previously reported.¹⁴

Patient Outcomes

The primary outcome for EchoCRT was the combined endpoint of all-cause mortality or first hospitalization for worsening HF. Secondary outcomes analyzed in this present substudy were HF hospitalization alone and all-cause mortality alone. Hospitalization for worsening HF was defined as a hospitalization for administration or augmentation of intravenous or oral HF therapy, including inotropes, diuretics, and/or vasodilators. Hospitalization was defined as a non-elective admission of at least one overnight stay. Therapeutic, non-elective interventional procedures were considered hospitalizations (such as percutaneous coronary interventions and cardiac surgery). Time to first event was counted from the time of randomization for the duration of the study. Follow-up was until the time the study was terminated.

Statistics

The study results were analyzed at the independent Statistical Centre at the Robertson Centre for Biostatistics, University of Glasgow. Baseline characteristics were reported as means and standard deviations for continuous variables (except BNP/NT-proBNP where medians and lower and upper quartiles were reported) and counts and percentages for categorical variables and treatment group comparisons were based on two-sample t-test (or Mann-Whitney test) and chi-square (or Fisher's exact) tests as appropriate. Hazard ratios and 95% confidence intervals were calculated from Cox proportional hazards models including treatment group as a covariate. Follow-up was censored at study closure, date of death, LV assist device implantation, heart transplant or withdrawal from the study or loss to follow-up whichever came first. Interactions between treatment effects and dyssynchrony subgroups were tested for in Cox models that

included treatment and dyssynchrony subgroup main effects and interaction terms. Time-to-event curves were estimated using the method of Kaplan and Meier.

Results

Echocardiographic Dyssynchrony at 6 Months

The EchoCRT trial was terminated early after interim analysis because of futility in reaching the primary endpoint and an observed increase in mortality in the CRT-On group. There were 614 patients with 6 month follow-up echocardiograms included in this substudy analysis. Their baseline dyssynchrony by randomization was similar as follows: TDI opposing wall delay (4 Chamber view) 89.1 ± 33.6 ms in CRT-On and 89.4 ± 38.9 ms for CRT-Off, TDI opposing wall delay (apical long axis view) 90.1 ± 36.3 for CRT-On and 87.7 ± 41.2 ms, Speckle tracking radial strain 217.1 ± 95.4 ms for CRT-On and 223.4 ± 101.7 ms for CRT-Off. Their baseline characteristics grouped by presence or absence of significant dyssynchrony on the 6 month follow-up echocardiogram appears in Table 1. All baseline clinical characteristics were similar in both groups except for a greater LVEDD in patients with persistent dyssynchrony (66.9 ± 7.70 mm versus 65.3 ± 6.98 mm, $p=0.02$). Baseline characteristics with $p<0.1$ by comparison of groups were LVEF ($27.2 \pm 5.42\%$ versus $28.2 \pm 5.40\%$, $p=0.51$) and QRS width 106.3 ± 12.1 ms versus 104.4 ± 12.9 ms, $p=0.91$). The proportion of patients randomized to CRT-On versus CRT-OFF had similar significant dyssynchrony at 6 months as follows:, 61% with CRT-On and 60 % with CRT-Off had persistent dyssynchrony by TDI in any view (≥ 80 ms), 45% with CRT-On and 51 % with CRT-Off had persistent dyssynchrony by radial strain (≥ 130 ms), and 76% with CRT-On and 77 % with CRT-Off had persistent dyssynchrony by either TDI or radial strain (Figure 3). In other words, overall 24% had resolution at 6 months of their significant baseline echocardiographic dyssynchrony required for study enrollment, regardless of being in CRT-On or CRT-Off groups.

Associations of Echocardiographic Dyssynchrony at 6 Months with Clinical Outcomes

The mean follow-up period was 19.4 months for all patients and 19.8 months for surviving patients. In this study cohort of 614 patients, 234 patients reached an end-point: 146 HF hospitalizations and 88 deaths. The CRT-On subgroup had 76 HF hospitalizations and 29 deaths and the CRT-Off subgroup had 70 HF hospitalizations and 18 deaths. This comparatively greater mortality in the CRT-On group is similar to as reported previously in EchoCRT.¹⁴ At 6 months, there were 469 patients (76%) with persistent dyssynchrony by either TDI longitudinal velocity (≥ 80 ms) or speckle tracking radial strain (≥ 130 ms) and 145 patients (24%) with improvement in baseline dyssynchrony with neither significant longitudinal nor radial dyssynchrony at 6 months. There was a significant association of persistent dyssynchrony with the primary outcome of HF hospitalization or death (HR= 1.54, 95% CI 1.03-2.30), $p=0.034$, Figure 4), and in particular with the secondary outcome of HF hospitalization alone (HR= 1.66, 95% CI 1.07-2.57, $p=0.023$). Persistent dyssynchrony was not associated with total mortality ($p=0.38$ HR=0.75, 95% CI 0.39-1.42). Regarding CRT-On versus CRT-Off subgroups, there were no significant interaction of treatment subgroup with dyssynchrony for the primary endpoint ($p = 0.14$) (Figure 5).

Association of Dyssynchrony at 6 Months with Heart Failure Hospitalization after Adjustment for Baseline Characteristics

We examined 24 baseline characteristics potentially associated with patient outcomes (Table 1). Patients were balanced with only 3 variables identified as potentially co-varying with 6 month echocardiographic dyssynchrony ($p<0.10$): LVEDD, LVEF and QRS width. After statistical adjustment for these, persistent dyssynchrony at 6 months remained significantly associated with HF hospitalization, HR= 1.57, (95% CI 1.01-2.44), $p=0.045$. After examining further, there was no impact of randomization groups of CRT-On versus CRT-Off and results were similar. There was also a trend toward persistent dyssynchrony to be associated with the combined end-point of HF hospitalization and death in the model further adjusted for LVEDD, LVEF, QRS width and

CRT treatment randomization, $p=0.06$, $HR= 1.47$, (95% CI 0.98-2.20).

Association of Longitudinal and Radial Dyssynchrony at 6 Months with Clinical Outcomes

Associations of clinical outcomes with longitudinal and radial dyssynchrony individually were then determined. There were 608 of 614 total patients (99%) overall with 6 month TDI data available. There was a significant association of persistent longitudinal dyssynchrony with HF hospitalization, $HR= 1.49$, (95% CI 1.05-2.12), $p=0.027$. (Figure 6A). For the primary end-point of total mortality or HF hospitalization, there was a trend toward an association of persistent longitudinal dyssynchrony, $HR= 1.37$, (95% CI 0.99 – 1.90), $p=0.061$, $HR=1.37$, (95% CI 0.99-1.90). There was no significant association of persistent longitudinal dyssynchrony with total mortality, $p=0.31$, $HR=0.74$, (95% CI=0.41-1.32). There was no evidence of an interaction between CRT-On and CRT-Off status and association between persistent longitudinal dyssynchrony at 6 months and the outcomes of HF hospitalization or death, $p = 0.67$), HF hospitalization alone ($p = 0.64$) or mortality alone ($p = 0.58$).

There were 536 of 614 total patients (87%) overall with 6 month speckle tracking radial strain data available. There was a significant association of persistent radial dyssynchrony with the primary outcome of HF hospitalization or death with a $HR= 1.43$, (95% CI 1.03 - 1.99), $p=0.032$. There was also a significant association of persistent radial dyssynchrony of the secondary outcome variable of HF hospitalization alone $HR= 1.53$, (95% CI 1.08-2.18), $p=0.018$. (Figure 6B). There was no significant association of persistent radial dyssynchrony with total mortality, $p=0.62$, $HR=1.15$, (95%CI 0.62-2.13). There was no evidence of an interaction between CRT-On and CRT-Off status and the association between CRT treatment and the primary outcome of HF hospitalization or death ($p = 0.41$), HF hospitalization alone ($p = 0.68$) or mortality alone ($p = 0.37$).

Association of Worsening Dyssynchrony at 6 months with Clinical Outcomes

There were 155 of 608 patients (25%) with increasing dyssynchrony by TDI longitudinal velocity from baseline to 6 months (increasing ≥ 30 ms). There was a significant association of worsening longitudinal dyssynchrony with the primary outcome of HF hospitalization or death with a HR= 1.42, (95% CI 1.02 – 1.97), $p=0.037$. There was also a significant association of worsening longitudinal dyssynchrony with HF hospitalization, HR = 1.46, 95%CI 1.03-2.06, $p=0.034$. (Figure 7A). Worsening longitudinal dyssynchrony was not associated with mortality, $p=0.788$. These results appeared unaffected by CRT with no interaction observed between randomization treatment (CRT-On vs. CRT-Off) and these clinical end-points ($p = 0.128$ and $p = 0.340$). There were 64 of 507 patients (13%) with worsening dyssynchrony by radial strain from baseline to 6 months (increasing ≥ 60 ms). There was a significant association of worsening radial dyssynchrony with the primary outcome of HF hospitalization or death with a HR= 1.62, (95% CI 1.06 – 2.49), $p=0.027$. There was also a highly significant association of worsening radial dyssynchrony with HF hospitalization with a HR = 1.81, 95% CI 1.16-2.81, $p=0.008$. (Figure 7B). Once again, there was no association of worsening dyssynchrony with mortality, $p=0.899$ and no interaction observed between randomization treatment and clinical end-points.

Discussion

This substudy of the EchoCRT randomized clinical trial of HF patients with narrow QRS width demonstrated that persistent or worsening echocardiographic dyssynchrony from baseline to 6 month follow-up was associated with unfavorable clinical outcomes, in particular HF hospitalizations. The *post hoc* observation that dyssynchrony on follow-up echocardiography was associated with patient outcome was similar in both randomization groups, and thus appeared unaffected by CRT. This study did not provide mechanistic evidence and these observations may be considered hypothesis generating. EchoCRT enrolled HF patients with relatively narrow QRS duration (<130 ms), LV dilatation, reduced LVEF, and baseline echocardiographic dyssynchrony, and concluded that CRT was not of benefit.¹⁴ All patients

required baseline echocardiographic dyssynchrony for entry into the trial. Of interest, 76% were observed to have persistent dyssynchrony at 6 months and 24% improved to having no significant dyssynchrony at follow-up. Improvement in dyssynchrony was similar in CRT-On and CRT-Off groups, and no interaction with treatment randomization was demonstrated. Importantly, persistent dyssynchrony at 6 months was significantly associated with the primary outcome variable of HF hospitalization or death and HF hospitalization alone. Even after adjusting for the potential confounding variables, persistent dyssynchrony remained significantly associated with HF hospitalization. As further evidence to support this association, both TDI longitudinal dyssynchrony and speckle tracking radial strain dyssynchrony at 6 months when examined separately were significantly associated with HF hospitalization, which was also unaffected by CRT randomization. Furthermore, increases in either TDI longitudinal or speckle tracking radial dyssynchrony from baseline to 6 months were significantly associated with both the primary outcome variable and in particular HF hospitalization alone. These consistent observations support echocardiographic dyssynchrony as potentially a new prognostic marker in HF patients with reduced LVEF and narrow QRS width, in particular for HF hospitalizations. Since these associations were similar in CRT-On and CRT-Off groups, our results suggest that echocardiographic dyssynchrony may possibly be a marker for unfavorable LV mechanics and more severe myocardial disease in patients with narrow QRS width.

Many previous investigations have focused on baseline echocardiographic dyssynchrony in HF patients with QRS widening before CRT as a marker for a more favorable response to CRT.^{4-9, 19, 21, 22} Several other studies in HF patients with QRS widening have reported dyssynchrony after CRT as a marker for unfavorable outcomes. Bleeker et al. demonstrated lack of improvement in TDI longitudinal velocity opposing wall delay assessed immediately after CRT was associated with lack of LV reverse remodeling at 6 months.²³ Auger et al. also reported the association of worsening dyssynchrony by TDI velocity after CRT with less LV reverse

remodeling and worse survival.²⁴ Saba et al. using an echo-guided LV lead placement strategy, demonstrated that patients who did not improve radial strain dyssynchrony had higher rates of death or HF hospitalization after CRT.²⁵ Stankovic et al. also showed that lack of improvement of dyssynchrony assessed by apical rocking was associated with less favorable clinical outcomes after CRT.²⁶ Furthermore, Doltra et al. recently showed that lack of improvements in septal flash, abnormal ventricular filling, or exaggerated interventricular dependence after CRT were associated with less LV reverse remodeling and patient survival.²⁷ Echocardiographic dyssynchrony after CRT in HF patients with QRS widening is also a marker for ventricular arrhythmias.^{28 29} Interesting, patients with severe HF and worsening dyssynchrony after CRT were shown to be at the greatest risk for serious ventricular arrhythmias.²⁹

There is much less reported on the significance of dyssynchrony in HF patients with narrow QRS duration unrelated to CRT. Mechanical dyssynchrony may likely represent different pathophysiological phenomena in patients with widened versus narrow QRS durations.³⁰ Yamada et al. also reported mechanical dyssynchrony to precede widening of the QRS complex as a marker for progression of myocardial disease in knockout murine surrogate of human cardiomyopathy.³¹ Tanaka et al. studied dyssynchrony in 201 HF patients with narrow QRS and acute non-ischemic cardiomyopathy. They observed dyssynchrony to be present in 54% at HF presentation which decreased to 12% at 6 month follow-up when treated with routine medical therapy.¹⁸ Improvements in LV dyssynchrony and cardiac function in non-ischemic disease were perhaps related to changes in myocardial inflammation which may have heterogeneous effects on regional contractility.¹⁸ Recent work has demonstrated that pattern of dyssynchrony by strain imaging might be more important than a delay in time-to-peak between segments in differentiating the electromechanical substrate that is responsive to CRT from pure mechanical delay resulting from regional contraction heterogeneity or scar that is unresponsive to CRT. Myocardial ischemic, infarction and scar represent other pathophysiologic basis for LV

dyssynchrony in patients with narrow QRS width.³² Accordingly, LV dyssynchrony may originate from different myocardial substrates, including an electromechanical substrate regional contraction delays from delayed electrical activation, and non-electrical dyssynchrony substrates, such as contraction heterogeneity or scar.¹⁶ The basis for improvements in LV dyssynchrony observed in the present substudy of HF patients with narrow QRS, including improvements in the control group is unknown. We may hypothesize that changes in LV dyssynchrony may have related to yet undefined factors affecting regional contractility or result from effects of medical therapy on LV reverse remodeling. Overall, EchoCRT patients received intensive medical therapy of agents with known effects on reverse remodeling; 95% were on an angiotensin converting enzyme inhibitor or an aldersterone receptor blocker and 97% were on beta-blocker therapy. Further investigation of factors influencing LV mechanical dyssynchrony in HF is warranted.

Limitations

It is a limitation that this study was confined to patients in the EchoCRT trial who had 6 month echocardiograms available for analysis. Since the study was terminated prematurely, several patients did not have 6 month echocardiograms performed. It is a limitation that dyssynchrony measures are limited to baseline and 6 month time points, so we are unable to exclude possible changes in dyssynchrony that may have occurred in the interim. A limitation was that dyssynchrony analysis was limited to peak-to-peak timing and further analysis of velocity or strain was not part of this present study. Another limitation is that speckle tracking echocardiography could not be performed on all patients and was available on 87%, similar to the yield on previous studies.^{6, 19} TDI data were available on 99% of patients. The advantage of speckle tracking strain over TDI velocity is that strain is less affected by passive motion or tethering, such as occurs in scar. It is a major limitation that scar as a source of dyssynchrony was not assessed by an alternate imaging technique, such as contrast cardiac magnetic resonance

imaging. It was a limitation that the definitions we used for worsening dyssynchrony were determined post hoc and there are no previous published criteria for worsening dyssynchrony in this unique population. Our major results were reported on persistent dyssynchrony using pre-defined criteria and findings on worsening dyssynchrony should be considered as supplemental. Future prospective study of criteria for worsening dyssynchrony is warranted. Another limitation was that the relationship of LV lead position to patient outcome was not part of the present study, but the associations of persistent or worsening dyssynchrony with clinical outcomes were similar in CRT-On and CRT-Off groups.²⁵ A significant limitation in previous studies has been variability of dyssynchrony measures.³³ This study limited variability by using a single ultrasound vendor and analysis software and a core echocardiography laboratory with documented favorable reproducibility. However, the interplay of variabilities in complex measurements including differences between measurements taken at baseline and 6 months are not clearly defined and remains a limitation.

Conclusions

Persistent or worsening echocardiographic dyssynchrony in HF patients with narrow QRS width and reduced LVEF at 6 month follow-up was associated with the combined end-point of HF hospitalizations or death and in particular HF hospitalizations alone, regardless of CRT-On or CRT-Off. Accordingly, improvement in dyssynchrony was associated with less HF hospitalizations or deaths. Persistent or worsening echocardiographic dyssynchrony appears to be a marker for disease severity in HF patients and has prognostic significance. The relative value of persistent dyssynchrony in comparison to established markers of HF prognosis are unknown and further prospective multivariable study is warranted.

Conflict of Interest Disclosures

The EchoCRT trial was sponsored by Biotronik, Inc. with an equipment grant from G.E.

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References

1. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, Messenger J. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;**346**(24):1845-53.
2. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;**350**(21):2140-50.
3. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;**352**(15):1539-49.
4. Bax JJ, Bleeker GB, Marwick TH, Molhoek SG, Boersma E, Steendijk P, van der Wall EE, Schalij MJ. Left ventricular dyssynchrony predicts response and prognosis after cardiac resynchronization therapy. *J Am Coll Cardiol* 2004;**44**(9):1834-40.
5. Gorcsan J, 3rd, Kanzaki H, Bazaz R, Dohi K, Schwartzman D. Usefulness of echocardiographic tissue synchronization imaging to predict acute response to cardiac resynchronization therapy. *Am J Cardiol* 2004;**93**(9):1178-81.
6. Gorcsan J, 3rd, Oyenuga O, Habib PJ, Tanaka H, Adelstein EC, Hara H, McNamara DM, Saba S. Relationship of echocardiographic dyssynchrony to long-term survival after cardiac resynchronization therapy. *Circulation* 2010;**122**(19):1910-8.
7. Gorcsan J, 3rd, Tanabe M, Bleeker GB, Suffoletto MS, Thomas NC, Saba S, Tops LF, Schalij MJ, Bax JJ. Combined longitudinal and radial dyssynchrony predicts ventricular response after resynchronization therapy. *J Am Coll Cardiol* 2007;**50**(15):1476-83.
8. Sogaard P, Egeblad H, Kim WY, Jensen HK, Pedersen AK, Kristensen BO, Mortensen PT. Tissue Doppler imaging predicts improved systolic performance and reversed left ventricular remodeling during long-term cardiac resynchronization therapy. *J Am Coll Cardiol* 2002;**40**(4):723-30.
9. Yu CM, Chau E, Sanderson JE, Fan K, Tang MO, Fung WH, Lin H, Kong SL, Lam YM, Hill MR, Lau CP. Tissue Doppler echocardiographic evidence of reverse remodeling and improved synchronicity by simultaneously delaying regional contraction after biventricular pacing therapy in heart failure. *Circulation* 2002;**105**(4):438-45.
10. Bax JJ, Abraham T, Barold SS, Breithardt OA, Fung JW, Garrigue S, Gorcsan J, 3rd, Hayes DL, Kass DA, Knuuti J, Leclercq C, Linde C, Mark DB, Monaghan MJ, Nihoyannopoulos P, Schalij MJ, Stellbrink C, Yu CM. Cardiac resynchronization therapy: Part 1--issues before device implantation. *J Am Coll Cardiol* 2005;**46**(12):2153-67.
11. Yu CM, Chan YS, Zhang Q, Yip GW, Chan CK, Kum LC, Wu L, Lee AP, Lam YY, Fung JW. Benefits of cardiac resynchronization therapy for heart failure patients with narrow QRS complexes and coexisting systolic asynchrony by echocardiography. *J Am Coll Cardiol* 2006;**48**(11):2251-7.
12. Beshai JF, Grimm RA, Nagueh SF, Baker JH, 2nd, Beau SL, Greenberg SM, Pires LA, Tchou PJ, Rethin QSI. Cardiac-resynchronization therapy in heart failure with narrow QRS complexes. *N Engl J Med* 2007;**357**(24):2461-71.
13. Bader H, Garrigue S, Lafitte S, Reuter S, Jais P, Haissaguerre M, Bonnet J, Clementy J, Roudaut R. Intra-left ventricular electromechanical asynchrony. A new independent predictor of severe cardiac events in heart failure patients. *J Am Coll Cardiol* 2004;**43**(2):248-56.
14. Ruschitzka F, Abraham WT, Singh JP, Bax JJ, Borer JS, Brugada J, Dickstein K, Ford I, Gorcsan J, 3rd, Gras D, Krum H, Sogaard P, Holzmeister J, Echo CRTSG. Cardiac-resynchronization therapy in heart failure with a narrow QRS complex. *N Engl J Med* 2013;**369**(15):1395-405.
15. Helm RH, Leclercq C, Faris OP, Ozturk C, McVeigh E, Lardo AC, Kass DA. Cardiac dyssynchrony analysis using circumferential versus longitudinal strain: implications for assessing cardiac resynchronization. *Circulation* 2005;**111**(21):2760-7.

16. Lumens J, Leenders GE, Cramer MJ, De Boeck BW, Doevendans PA, Prinzen FW, Delhaas T. Mechanistic evaluation of echocardiographic dyssynchrony indices: patient data combined with multiscale computer simulations. *Circ Cardiovasc Imaging* 2012;**5**(4):491-9.
17. Prinzen FW, Hunter WC, Wyman BT, McVeigh ER. Mapping of regional myocardial strain and work during ventricular pacing: experimental study using magnetic resonance imaging tagging. *J Am Coll Cardiol* 1999;**33**(6):1735-42.
18. Tanaka H, Tanabe M, Simon MA, Starling RC, Markham D, Thohan V, Mather P, McNamara DM, Gorcsan J, 3rd. Left ventricular mechanical dyssynchrony in acute onset cardiomyopathy: association of its resolution with improvements in ventricular function. *JACC Cardiovasc Imaging* 2011;**4**(5):445-56.
19. Suffoletto MS, Dohi K, Cannesson M, Saba S, Gorcsan J, 3rd. Novel speckle-tracking radial strain from routine black-and-white echocardiographic images to quantify dyssynchrony and predict response to cardiac resynchronization therapy. *Circulation* 2006;**113**(7):960-8.
20. Gorcsan J, 3rd, Abraham T, Agler DA, Bax JJ, Derumeaux G, Grimm RA, Martin R, Steinberg JS, Sutton MS, Yu CM. Echocardiography for cardiac resynchronization therapy: recommendations for performance and reporting--a report from the American Society of Echocardiography Dyssynchrony Writing Group endorsed by the Heart Rhythm Society. *J Am Soc Echocardiogr* 2008;**21**(3):191-213.
21. Hara H, Oyenuga OA, Tanaka H, Adelstein EC, Onishi T, McNamara DM, Schwartzman D, Saba S, Gorcsan J, 3rd. The relationship of QRS morphology and mechanical dyssynchrony to long-term outcome following cardiac resynchronization therapy. *Eur Heart J* 2012;**33**(21):2680-91.
22. Risum N, Williams ES, Khouri MG, Jackson KP, Olsen NT, Jons C, Storm KS, Velazquez EJ, Kisslo J, Bruun NE, Sogaard P. Mechanical dyssynchrony evaluated by tissue Doppler cross-correlation analysis is associated with long-term survival in patients after cardiac resynchronization therapy. *Eur Heart J* 2013;**34**(1):48-56.
23. Bleeker GB, Mollema SA, Holman ER, Van de Veire N, Ypenburg C, Boersma E, van der Wall EE, Schalij MJ, Bax JJ. Left ventricular resynchronization is mandatory for response to cardiac resynchronization therapy: analysis in patients with echocardiographic evidence of left ventricular dyssynchrony at baseline. *Circulation* 2007;**116**(13):1440-8.
24. Auger D, Bleeker GB, Bertini M, Ewe SH, van Bommel RJ, Witkowski TG, Ng AC, van Erven L, Schalij MJ, Bax JJ, Delgado V. Effect of cardiac resynchronization therapy in patients without left intraventricular dyssynchrony. *Eur Heart J* 2012;**33**(7):913-20.
25. Saba S, Marek J, Schwartzman D, Jain S, Adelstein E, White P, Oyenuga OA, Onishi T, Soman P, Gorcsan J, 3rd. Echocardiography-guided left ventricular lead placement for cardiac resynchronization therapy: results of the Speckle Tracking Assisted Resynchronization Therapy for Electrode Region trial. *Circ Heart Fail* 2013;**6**(3):427-34.
26. Stankovic I, Aaronson M, Smith HJ, Voros G, Kongsgaard E, Neskovic AN, Willems R, Aakhus S, Voigt JU. Dynamic relationship of left-ventricular dyssynchrony and contractile reserve in patients undergoing cardiac resynchronization therapy. *Eur Heart J* 2014;**35**(1):48-55.
27. Doltra A, Bijmens B, Tolosana JM, Borrás R, Khatib M, Penela D, De Caralt TM, Castel MA, Berrueto A, Brugada J, Mont L, Sitges M. Mechanical abnormalities detected with conventional echocardiography are associated with response and midterm survival in CRT. *JACC Cardiovasc Imaging* 2014;**7**(10):969-79.
28. Kutiyifa V, Pouleur AC, Knappe D, Al-Ahmad A, Gibinski M, Wang PJ, McNitt S, Merkely B, Goldenberg I, Solomon SD, Moss AJ, Zareba W. Dyssynchrony and the risk of ventricular arrhythmias. *JACC Cardiovasc Imaging* 2013;**6**(4):432-44.
29. Haugaa KH, Marek JJ, Ahmed M, Ryo K, Adelstein EC, Schwartzman D, Saba S, Gorcsan J, 3rd. Mechanical dyssynchrony after cardiac resynchronization therapy for severely symptomatic heart failure is associated with risk for ventricular arrhythmias. *J Am Soc Echocardiogr* 2014;**27**(8):872-9.
30. Kass DA. An epidemic of dyssynchrony: but what does it mean? *J Am Coll Cardiol* 2008;**51**(1):12-7.

31. Yamada S, Arrell DK, Kane GC, Nelson TJ, Perez-Terzic CM, Behfar A, Purushothaman S, Prinzen FW, Auricchio A, Terzic A. Mechanical dyssynchrony precedes QRS widening in ATP-sensitive K(+) channel-deficient dilated cardiomyopathy. *J Am Heart Assoc* 2013;**2**(6):e000410.
32. Manka R, Kozerke S, Rutz AK, Stoeck CT, Boesiger P, Schwitter J. A CMR study of the effects of tissue edema and necrosis on left ventricular dyssynchrony in acute myocardial infarction: implications for cardiac resynchronization therapy. *J Cardiovasc Magn Reson* 2012;**14**:47.
33. Chung ES, Leon AR, Tavazzi L, Sun JP, Nihoyannopoulos P, Merlino J, Abraham WT, Ghio S, Leclercq C, Bax JJ, Yu CM, Gorcsan J, 3rd, St John Sutton M, De Sutter J, Murillo J. Results of the Predictors of Response to CRT (PROSPECT) trial. *Circulation* 2008;**117**(20):2608-16.

Figure Legends

Figure 1. Flow chart of patients included in this subgroup analysis from all patients randomized in the EchoCRT trial.

Figure 2. Representative echocardiographic examples of study patients with (A) persistent dyssynchrony and (B) improved dyssynchrony at 6 months. At Baseline, Patient A had tissue Doppler longitudinal peak velocity delay (arrows) of 140 ms within the ejection interval (top row left) and speckle tracking radial strain septal (yellow line) to posterior wall (purple line) delay (arrows) of 197ms (2nd row left). At 6 month follow-up Patient A had persistent longitudinal velocity delay (arrows) of 150ms (top row right) and radial strain delay (arrows) of 184ms (2nd row right). At Baseline, Patient B had longitudinal velocity delay (arrows) of 139 ms (3rd row left) and radial strain delay (arrows) of 165ms (bottom row left). At 6 month follow-up, Patient B had improvement in longitudinal velocity delay (arrows) to 14 ms (3rd row right) and radial strain delay (arrows) to 27 ms (bottom row right). AVO= aortic valve opening, AVC = aortic valve closure.

Figure 3. Bar graphs of frequency of echocardiographic dyssynchrony at 6 months after randomization in the EchoCRT trial. TDI = tissue Doppler imaging.

Figure 4. Kaplan-Meier plots of all patients demonstrating the significant association of echocardiographic dyssynchrony at 6 months with the primary outcome variable of death or hospitalization for heart failure. mo. = months

Figure 5. Kaplan-Meier plots of subgroups divided by randomization to cardiac resynchronization therapy (CRT) on or off and echocardiographic dyssynchrony at 6 months. There was no significant interaction observed with CRT and echocardiographic dyssynchrony on the primary outcome or other outcome variables. Dys. = dyssynchrony, mo. = months

Figure 6. Kaplan-Meier plots demonstrating the significant association echocardiographic dyssynchrony at 6 months by (A) longitudinal velocity or (B) radial strain with heart failure hospitalization in all patients. Dys = dyssynchrony, mo. = months.

Figure 7. Kaplan-Meier plots demonstrating the significant association of worsening echocardiographic dyssynchrony at 6 months by (A) longitudinal velocity or (B) radial strain with heart failure hospitalization in all patients. mo. = months.

Table 1: Baseline characteristics of all 614 patients grouped by presence or absence of echocardiographic dyssynchrony at 6 month follow-up.

| | Patients without Dyssynchrony at 6 mo. (n=145) | Patients with Dyssynchrony at 6 mo. (n=469) | P |
|--|---|--|----------|
| Age (years) | 58.6 (11.81) | 58.1 (12.78) | 0.686 |
| Male Sex | 111 (76.55%) | 334 (71.22%) | 0.209 |
| QRS width (ms) | 104.4 (12.90) | 106.3 (12.08) | 0.091 |
| Walking distance (m) | 327.0 (124.11) | 330.6 (115.32) | 0.744 |
| Quality of life score | 52.3 (24.41) | 50.3 (24.15) | 0.400 |
| NYHA Class (II, III, IV) | 2.07%, 95.17%, 2.76% | 3.20%, 93.39%, 2.56% | |
| BNP (pg/ml) | 265.5 (92.00) | 224.0 (97.50) | 0.653 |
| NT-proBNP (pg/ml) | 984.0 (402.00) | 1154.0 (465.50) | 0.643 |
| Systolic Blood Pressure (mmHg) | 119.3 (21.56) | 119.7 (18.62) | 0.821 |
| Diastolic Blood Pressure (mmHg) | 73.2 (13.30) | 72.9 (11.43) | 0.742 |
| Body mass index (kg/m ²) | 30.4 (7.42) | 31.2 (13.32) | 0.532 |
| Ischemic disease | 77 (53.10%) | 254 (54.27%) | 0.805 |
| Hypertension | 98 (68.53%) | 306 (65.52%) | 0.506 |
| Prior stroke or TIA | 14 (9.72%) | 50 (10.75%) | 0.725 |
| Diabetes | 50 (34.48%) | 181 (38.68%) | 0.363 |
| Chronic lung disease | 27 (18.75%) | 90 (19.31%) | 0.881 |
| Chronic kidney disease | 21 (14.58%) | 63 (13.49%) | 0.739 |
| LVEF Biplane (%) | 28.2 (5.40) | 27.2 (5.42) | 0.051 |
| LV end diastolic diameter (mm) | 65.3 (6.98) | 66.9 (7.70) | 0.020 |
| Dyssynchrony Qualification: | | | 0.215 |
| TDI only | 33 (22.76%) | 112 (23.93%) | |
| Radial strain only | 39 (26.90%) | 94 (20.09%) | |
| Both TDI and radial strain | 73 (50.34%) | 262 (55.98%) | |
| ACE inhibitor or ARB | 139 (95.86%) | 446 (95.10%) | 0.704 |
| Aldosterone antagonist | 83 (57.24%) | 272 (58.00%) | 0.872 |
| Beta-blocker | 141 (97.24%) | 454 (96.80%) | 1.000 |
| Diuretic agent | 121 (83.45%) | 409 (87.21%) | 0.250 |
| NYHA = New York Heart Association, BNP = brain natriuretic peptide, TIA = transient ischemic attack, LV = left ventricular, EF=ejection fraction, TDI = tissue Doppler imaging, ACE = angiotensin converting enzyme, ARB = angiotensin II receptor blockers, mo = months | | | |